

REMARKS

Applicants have carefully reviewed and considered the Office Action mailed on June 1, 2007, and the references cited therewith. Reconsideration and withdrawal of the rejections of the pending claims is respectfully requested.

Claims 6, 10-14, 44-53, and 55-56 are pending in this application.

I. The Rejection of the Claims under 35 U.S.C. §103

Claims 6, 10-14, 44-53 and 55-56 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Willmore et al. (U.S. Patent No. 5,248,697) in view of Shinal et al. (WO 00/69470) in view of Good et al. (U.S. Patent No. 6,666,811). This rejection is respectfully traversed.

Radiation therapy has been an effective treatment for breast cancer for many years. Radiation therapy kills cancer cells and healthy cells, including skin cells, in the treatment area. The skin in the area damaged by radiation may become reddened, dry, itchy, sunburned, or blistered and peeling (a condition called "moist desquamation"). Skin breakdown may occur, which may lead to an infection. Radiation injury to the skin causes significant pain and discomfort to the patient, impacts patient quality of life, and, in some cases, requires curtailing treatment. See specification, page 51, line 8 through page 52, line 10; see, www.radiologyinfo.org, "Breast Cancer" (printed copy attached herewith); see, www.cancer.gov, "Radiation Therapy Side Effects and Ways to Manage Them" (printed copy attached herewith).

Applicants have made the discovery that breast tissue can be protected against damage from radiation therapy by orally administering an aqueous composition comprising glutamine and carbohydrate to a patient afflicted with breast cancer and treated with radiation therapy. Applicants' method protects the breast tissue or associated upper body tissue against damage from the radiation therapy, so that the subject can be treated with a higher dose of radiation and/or treated with radiation for a longer time. It is highly significant that the glutamine and carbohydrate can be effective to protect non-mucosal tissue when given orally.

Applicants respectfully assert that the Examiner has not met the requirements for establishing a *prima facie* case of obviousness for the rejection of presently pending claims 6, 10-14, 44-53 and 55-56. The factual inquiries for the determination of obviousness, as set forth

in Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), are as follows: 1) determine the scope and contents of the prior art; 2) ascertain the differences between the prior art and the claims at issue; and 3) resolve the level of ordinary skill in the pertinent art; and 4) evaluate the evidence of secondary considerations. Id. See also M.P.E.P. §2141; KSR International, Co. v. Teleflex Inc. et al., 127 S. Ct. 1727; 167 L. Ed. 2d 705; 82 U.S.P.Q.2D 1385 (2007). For the reasons presented hereinbelow, Applicants assert that the Examiner has not established a *prima facie* case of obviousness.

Additionally, the Examiner's allegation that Applicants failed to argue the deficiency of the combination of the references, and only argued the deficiencies of the references individually is specifically disputed. The Response contained a section (D) that specifically argued the failure of the combined teachings of the references to suggest the claimed method. This section is essentially reproduced below.

Furthermore, the last Response also contained a lengthy paragraph setting forth secondary considerations of non-obviousness that must be considered when resolving the obviousness question. This evidence, which goes to long-felt need, was not even mentioned by the Examiner in his dismissal of the present claims as *prima facie* obvious in view of the art.

A. Wilmore (U.S. Patent No. 5,248,697)

The Wilmore '697 patent discloses methods for maintaining or enhancing tissue or plasma levels of glutathione in a mammal by administering supranormal amounts of glutamine (or glutamine equivalents). Large amounts of glutamine are given with the purpose of preventing a reduction in tissue glutathione levels associated with oxidative injury to the tissue of a mammal.

The Examiner concedes that Wilmore does not teach the co-administration of carbohydrate and glutamine in radiation therapy, and that Wilmore does not teach the utilization of higher dosages of radiation because of the protective effects of the methods claimed by Applicants. See Office Action, page 3, second para.

In fact, Wilmore discloses radiation therapy for the treatment of cancer in only general terms. See Wilmore, col. 2, lines 46-57; col. 5, line 58 through col. 6, line 2. Although the Examiner relies on Wilmore at col. 7, line 66 through col. 8, line 9 as teaching the use of

radiation therapy in breast cancer patients. Applicants note that that section actually describes a chemotherapy agent, SFU, as a treatment for several carcinomas, including breast cancer. Thus, Wilmore does not teach the administration of glutamine to protect against breast or upper body tissue damage from radiation therapy administered to breast cancer patients.

The method of Wilmore is not intended to be practiced by oral administration of glutamine. To begin, the terms "enteral" and "parenteral," as defined in Wilmore, do not include the term "oral" or anything arguably considered "oral." See Wilmore at col. 5, lines 53-57. Although Wilmore mentions that glutamine can be incorporated into the diet of a patient, the phrase "incorporation into the diet," without any additional definition, does not equate to "oral administration," but rather to incorporation into a "liquid diet" administered by enteral or parenteral feeding. Moreover, in each of Wilmore's three examples, the glutamine is given parenterally.

While the Examiner cites Col. 6, lines 22-48 as disclosing the "oral" administration of glutamine, the only disclosure in Wilmore relating to the "oral" administration of glutamine is directed to the use of glutamine following poisoning, not to its use during or following radiation treatment for cancer of any type. The word "oral" is used only once (see col. 6, lines 45-48): "The route of administration will depend upon the severity of the poisoning, and an initial intravenous administration can be followed by subsequent oral doses, either alone or with food. Thus, at most, this paragraph discloses a combination of intravenous administration and oral dosing, to treat a subject that has been acutely poisoned.

The very next sentence states "[t]he administration of glutamine can be by enteral or parenteral means," and is followed by specifics and details on enteric and parenteral administration. See Wilmore, col. 6, lines 49-61. Wilmore continues, stating that "[g]lutamine can be administered either alone or as a dietary supplement. When used as a dietary supplement, the glutamine can be mixed with an existing enteral or parenteral diet prior to administration to the patient." See col. 6, lines 62-65. Thus, when the entire disclosure of Wilmore is considered, it is evident that the methods in Wilmore are not intended to be carried out by the oral administration of glutamine.

B. Shinal et al.

Shinal et al. disclose compositions and methods for increasing cellular uptake of bioactive agents into mammalian cells upon contact of the cells with glutamine and carbohydrate. The compositions comprise an aqueous vehicle, a bioactive agent and carbohydrate. See Shinal et al. p. 3, lines 4-19. The bioactive agents are molecules that exert a therapeutic or nutritive effect on a mammal after absorption of an effective amount of the molecule by the target cells. *Id.*, at page 5, lines 27-29.

However, the only use disclosed in Shinal et al. for their glutamine and carbohydrate compositions is to prevent or treat oral, nasal and esophageal lesions. See Shinal et al., p. 11, lines 25-29. There is no disclosure in Shinal et al. of orally administering an aqueous composition of glutamine and carbohydrate for the protection of a tissue remote from the administration site such as breast or upper body tissue. In fact, neither Wilmore nor Shinal et al. disclose any effect of glutamine on breast tissue or upper body tissue. Shinal et al. also do not disclose the use of their methods and compositions to protect breast or upper body tissue from radiation damage so that the patient can be treated with higher doses of radiation or treated with radiation for a longer period of time.

C. Good et al.

Good et al. teach methods of directed radiation therapy using radioactive implants to effectively control tumors without harming or injuring immediately adjacent tissues. See Good et al., col. 62, lines 44-45; col. 107, lines 62-65. Thus, Good et al. teach away from the administration of an exogenous chemical agent that protects normal tissues from radiation damage, while not similarly protecting cancerous tissue. One of ordinary skill in the art would not be motivated by Good et al. to use glutamine as an adjuvant to radiotherapy treatment. Instead, one of skill in the art would be led to use the radioimplants of Good et al. to treat cancer so that tumors can be controlled more effectively than conventional radiotherapy, without harm to adjacent tissues.

D. The combination of references

As stated by the Supreme Court in *KSR v. Teleflex*, “[t]he question is not whether the combination was obvious to the patentee but whether the combination was obvious to a person with ordinary skill in the art.” *KSR International, Co. v. Teleflex Inc. et al.*, 127 S. Ct. 1727; 167 L. Ed. 2d 705; 82 U.S.P.Q.2D 1385 (2007). Applicants assert that it is not obvious for a person of ordinary skill in the art to combine selected elements of the cited art, so as to yield the method set forth in the presently pending claims.

There is no logical reason that one of ordinary skill in the art would combine the teachings of Wilmore with Shinal et al. and Good et al. to solve the problem that Applicants have solved. It is respectfully submitted that one in possession of Wilmore and Shinal et al. might be motivated to parenterally or orally administer a mixture of glutamine and carbohydrate to a cancer patient to protect the patient's gastrointestinal tract tissue against the effects of cancer treatment. The parenteral administration of glutamine to "reduce or prevent starvation – or radiation associated with oxidative damage to tissues" as disclosed generally in Wilmore would not lead the art worker to administer glutamine orally to achieve this effect in the tissue of the breast or associated external tissue of a breast cancer patient treated with radiation. The references simply do not disclose or suggest that the oral ingestion of glutamine plus carbohydrate would have any effect any specific body tissue other than oral, nasal or esophageal tissue. Contrary to the assertion of the Examiner, Good et al. would not motivate one of ordinary skill in the art to treat any type of cancer with higher than normal doses of radiation in combination with anything other than the implants taught by Good et al.

The references, taken together or considered separately, do not suggest that orally administered glutamine would have any impact on breast or upper body tissue, let alone provide the beneficial effect of reducing the well-known side effects of radiation therapy on normal skin. For these reasons, a combination of Wilmore with Shinal et al. and Good et al. would not permit the art worker to arrive at Applicants' invention.

In view of the fact that the prior art does not even mention treatment/pre-treatment of breast cancer patients undergoing radiation, the Examiner is urged to consider that the presently-claimed method would not even be "obvious-to-try" in view of the large number of different types of cancer and tissues internal and external, that are affected by radiation therapy. Even if

the prior art would render it obvious to try to reduce radiation damage to breast and associated upper body tissue, the Examiner is urged that there would be no reasonable expectation of success. "[T]o have a reasonable expectation of success, one must be motivated to do more than merely to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful."

Medichem, S.A. v. Rolabo, S.L., 437 F.3d 1157, 1165 (Fed. Cir. 2006). It requires more than routine experimentation to evaluate the current oral formulation on a particular class of cancer patients undergoing arduous therapy, particularly when the prior art teaches merely to pursue a "general approach that [seems] to be a promising field of experimentation" or "[gives] only general guidance as to the particular form of the claimed invention or how to achieve it [as does Wilmore]." In re O'Farrell, 853 F.2d 894, 903 (Fed. Cir. 1993).

Moreover, the Graham obviousness standards require an evaluation of the evidence of secondary considerations. See Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966); Ruiz v. AB Chance Co., 234 F.3d 654, 667 (Fed. Cir. 2000) ("Our precedents clearly hold that secondary considerations when present, must be considered in determining obviousness"). Evidence that an invention satisfied a long-felt need is pertinent to the question of obviousness. See W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 220 U.S.P.Q 303 (Fed. Cir. 1983).

In the present matter, the painful side effects of radiation therapy to the skin of breast cancer patients are well-known. See, www.radiologyinfo.org, "Breast Cancer" (printed copy attached herewith); see, www.cancer.gov, "Radiation Therapy Side Effects and Ways to Manage Them" (printed copy attached herewith). Prior to Applicants' invention, breast cancer patients undergoing radiation therapy had no effective options for treating radiation-damaged skin. Patients were advised to "be gentle" on their skin, or not to wear tight clothes or to use soft fabrics in order to not further irritate the damaged skin. See www.cancer.gov, "Radiation Therapy Side Effects and Ways to Manage Them," at page 13. In addition, there were no medically recommended options for preventing breast tissue damage prior to radiation therapy. Applicants' composition protects the breast tissue or associated upper body tissue against damage from the radiation therapy, so that the subject can be treated with a higher dose of radiation

and/or treated with radiation for a longer time. Applicants' discovery that breast tissue can be protected against damage from radiation therapy by orally administering an aqueous composition of glutamine and carbohydrate to a patient afflicted with breast cancer and treated with radiation therapy fulfills an important, long-felt need.

These references, either alone or taken in combination, do not render the presently claimed invention obvious. Therefore, withdrawal of this rejection is appropriate and Applicants respectfully request that the rejection under 35 U.S.C. ' 103(a) be withdrawn.

II. The Double Patenting Rejection

Claims, 6, 10-14, 44-52 and 55-56 were rejected under the judicially created doctrine of double patenting over claim 1 of U.S. Patent No. 7,186,517, in view of Shinal et al. (WO 00/69470) and Good et al. (U.S. Patent No. 6,666,811). This rejection is respectfully traversed.

As set forth in the section of the M.P.E.P. on obviousness-type double patenting, the present situation is one in which the claims of an application are subject to rejection over the claims of an issued patent having a later effective filing date. M.P.E.P. § 804(II)(B)(1)(b) (8th ed., rev. 5, 2006). Thus, the claims in question are subject to a two-way test for obviousness. In the present case, the requirements for a two-way obviousness test are fully met. Applicants could not have filed the claims in the same application because the monitoring test claimed in the '517 patent was invented after the tissue protection method claimed in the present application. Also, the ownership of the '517 patent and the present application are not the same. The requirement for "administrative delay" is moot here, because the '517 patent was examined in a different Group Art Unit. Furthermore, there is no evidence that Applicants have not prosecuted this application diligently, or have attempted to delay its issuance. If the two-way test is applied, it is clear that the monitoring method is patentably distinct from the method of the present claims, as it requires determining the presence of a marker protein that is not disclosed or suggested in the present claims or specification. Therefore, withdrawal of this rejection is appropriate and is respectfully requested.

RESPONSE UNDER 37 CFR § 1.116

Serial Number: 10/633,402

Filing Date: August 1, 2003

Title: TREATMENT OF CANCER WITH GLUTAMINE

Page 12

Dkt: 781.020US1

CONCLUSION

Applicants respectfully submit that the claims are in condition for allowance, and notification to that effect is earnestly requested. Alternatively, withdrawal of the obviousness-type double patenting rejection will reduce the issues to be decided on Appeal. The Examiner is invited to telephone Applicants' attorney at (612) 373-6903 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

V. SUZANNE KLIMBERG ET AL.

By their Representatives,

SCHWEGMAN, LUNDBERG, WOESSNER & KLUTH, P.A.
P.O. Box 2938
Minneapolis, MN 55402
(612) 373-6903

Date: June 24, 2008

By Warren D. Woessner
Warren D. Woessner
Reg. No. 30,440

CERTIFICATE UNDER 37 CFR § 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 24th day of June 2008.

Name: PATRICIA A. HULTMAN

Signature: Patricia A. Hultman